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Review Article

Sleep and major depressive disorder: a review of non-pharmacological chronotherapeutic treatments for unipolar depression☆

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ABSTRACT

Depression is a significant public health issue, made worse by the absence of response to antidepressant medications by many patients. Given the high degree of overlap between sleep and circadian complaints and depression, chronotherapies are a promising avenue for novel, effective, and fast-acting treatments for depression.

A critical literature review was conducted of bright light therapy (BLT) as a treatment for unipolar depression. Additionally, a separate critical literature review was also conducted of several promising, non-pharmacological, combination chronotherapeutic treatments, including BLT, sleep deprivation/wake therapy, and sleep phase advance.

Results of BLT as a treatment for depression are encouraging, especially when used as an adjunct to antidepressant medications. It may also be desirable in special populations, such as geriatric and perinatal patients. Overall, results from combination chronotherapies are encouraging, though none has strong empirical support. Combining chronotherapies is an avenue of treatment which should be further explored.

1. Introduction

With a 16% lifetime prevalence, depression is a significant public health issue involving widespread distress and impairment in daily functioning [1]. Antidepressant medications (ADMs) are often the first-line treatments that physicians and psychiatrists turn to in order to combat this disorder. Unfortunately, many ADMs have small effect sizes relative to placebo [2], and ADMs may take several weeks to develop full therapeutic benefits [3–5]. Additionally, ADMs may be undesirable in some patients (such as geriatric patients who often have a variety of prescriptions, some of which may be associated with antidepressant contraindication) and perinatal women, who may wish to avoid medication while pregnant or breastfeeding. There is a clear need for additional evidence-based non-pharmacological treatments for depression which are not only effective, but fast-acting. Given the high frequency with which sleep and circadian disturbances are reported in depressed individuals, that increased sleep and circadian complaints or alterations are predictive of more negative treatment outcomes, and that circadian shifts can be associated with more severe depression [6–10], it follows that treatments targeting these systems may improve depression itself.

Naturalistic studies have highlighted a relationship between daily rhythms, habitual light exposure, and mood. People with higher habitual light exposure show elevated mood and lower likelihood of depression [11,12]. Bright light therapy (BLT) has been used for seasonal affective (depressive) disorder (SAD) for decades [13], and has more recently been shown to be a promising treatment for non-seasonal major depressive disorder [14,8,15]. BLT has been robustly demonstrated to be a safe, effective and well-tolerated treatment, both alone and in conjunction with ADMs for SAD [16]. Until recently, however, there has not been robust evidence for its efficacy in treating non-seasonal depression [17–22]. This paper reviews the use of BLT to treat non-seasonal, unipolar major depressive disorder. Additionally, this paper will separately

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Abbreviations

ADM	Antidepressant medication
BDI	Beck depression inventory
BLT	Bright light therapy
CBT-I	Cognitive behavioural therapy for insomnia
CSSRS	Columbia suicide severity scale
DSM	Diagnostic and statistical manual of mental disorders
GDS	Geriatric depression scale
HAM-D	Hamilton depression rating scale
ICD	International classification of diseases
MADRS	Montgomery Asberg depression rating scale
NNT	Number needed to treat
QIDS-SR	Quick inventory of depressive symptoms – self report 16
RCT	Randomized controlled trial
RDC	Research diagnostic criteria
SAD	Seasonal affective disorder
SDT	Sleep deprivation therapy
SIGH-SAD	Structured interview guide for the HAM-D – seasonal affective disorders
TSD	Total sleep deprivation

review research on combination non-pharmacological, sleep-focused treatments for unipolar, non-seasonal depression, including sleep deprivation therapy (also known as wake therapy), BLT, and sleep phase advance.

2. Literature search methods

2.1. Bright light therapy review

PubMed and PsycINFO were systematically searched, with English-language articles published prior to December 11, 2017 eligible for inclusion. Initial search terms included "bright light," depression, and depress*. Following identification of initial articles, relevant references from these initial articles were also included as appropriate. For article inclusions and exclusions, see Fig. 1. Articles were considered for inclusion if they met the following criteria: (1) primary research article in a peer-reviewed journal; (2) main participant sample was depressed; (3) main participant sample did not include individuals with a diagnosis of bipolar depression (given the potential differential response to light therapy (eg, [23] Deltito et al., [23]) or SAD, unless results were given separately by diagnosis; (4) main participant sample was not comprised of individuals with a primary health concern (eg, cancer, Parkinson's, anorexia); (5) depression outcomes were reported; (6) BLT was used; and if (7) there were five or more adult (human) subjects. A meta-analysis was not performed due to limited statistical power as a result of methodological variation and a small number of studies. Given study differences in criteria for response and remission, as well as in reporting outcomes such as effect sizes, overall values for likely effectiveness were not provided in the present manuscript. Instead, outcomes of the reviewed studies were reported as they were presented in the original manuscript.

Depression outcome variables of studies included in this review include the Beck Depression Inventory (BDI), the Geriatric Depression Scale (GDS), the Hamilton Depression Rating Scale (HAM-D) and modifications thereof, the Montgomery-Asberg Depression Rating Scale (MADRS), the Quick Inventory of Depressive Symptoms – Self Report 16 (QIDS-SR), the Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorders (SIGH-SAD), and the Zung Self-Rating Depression Scale. Lux-hours were calculated by multiplying the brightness of the supplied bright light (lux) by the number of hours the patients received the treatment (hours); for example, a 10,000 lux treatment for 30 min would constitute 5000 lux-hours. While this is an approximate manner of standardizing treatments for comparison purposes, light timing and duration is also an important element of BLT which is likely to have treatment implications.

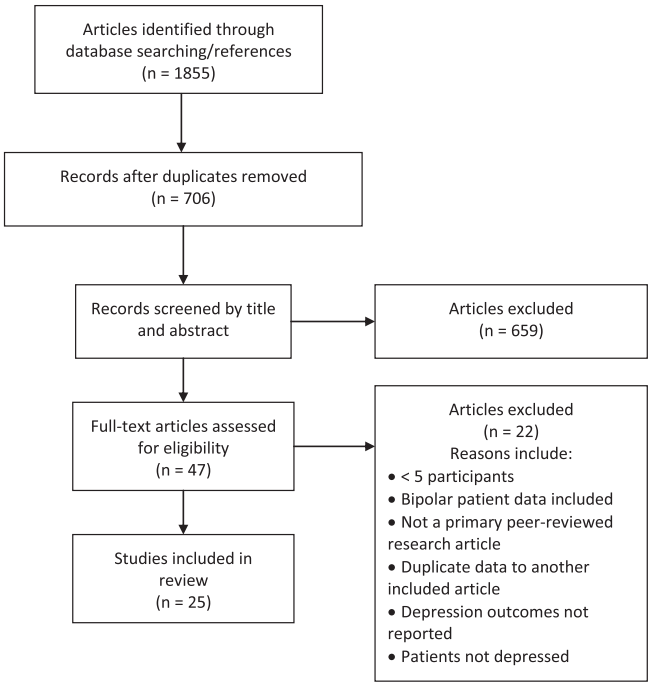

Fig. 1. BLT review flow diagram.

2.2. Combined chronotherapeutics review

PubMed and PsycINFO were systematically searched, with English-language articles published prior to January 1, 2018 eligible for inclusion. Initial search terms included "bright light", depression, depress*, "wake therapy", "phase advance", and "sleep deprivation", in various permutations. For article inclusions and exclusions, please see Fig. 2. Articles were considered for inclusion if they met the following criteria: (1) primary research article in a peer-reviewed journal; (2) main participant sample was depressed; (3) main participant sample did not include individuals with a diagnosis of bipolar depression or SAD, unless results were given separately by diagnosis; (4) main participant sample was not comprised of individuals with a primary health concern (eg, cancer, Parkinson's, anorexia); (5) depression outcomes were reported; (6) a combination of any of the following was used: BLT, sleep phase advance, wake therapy/sleep deprivation; and (7) there were five or more adult (human) subjects. A meta-analysis was not performed due to limited statistical power as a result of methodological variation and a small number of studies. Given study differences in criteria for response and remission, as well as in reporting outcomes such as effect sizes, overall values for likely effectiveness were not provided in the present manuscript. Instead, outcomes of the reviewed studies were reported as they were presented in the original manuscript. Depression outcome variables of studies included in this review also include the BDI, the GDS, the HAM-D and modifications thereof, the MADRS, the SIGH-SAD, and the Zung Self-Rating Depression Scale, as well as the Columbia Suicide

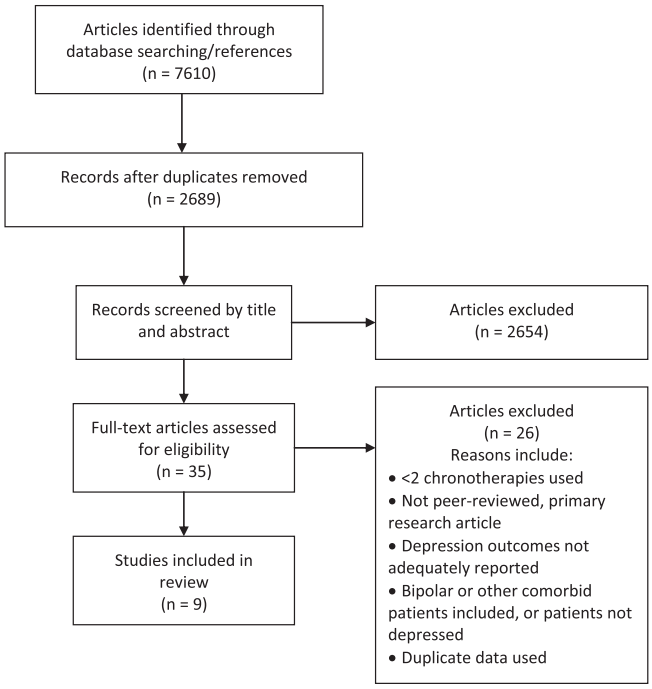

Fig. 2. Combined chronotherapeutics review flow diagram.

Severity Scale (CSSRS). Lux-hours were calculated in the same fashion as above.

3. Bright light therapy (BLT)

Eighteen of the studies (600 total patients, 15 with randomized controlled trial (RCT) elements, four with within-subjects elements) included in this review studied the effects of BLT on unipolar non-seasonal depression in the general population (Tables 1A and B). Studies range from 1985 to 2016. Average daily lux-hours was 7278 (calculated using lowest indicated lux hours per included study). Mean treatment duration was 18 consecutive days.

3.1. Bright light therapy as an adjunct to antidepressant medications

Of these 17 studies, nine investigated the use of BLT to augment treatment response to ADMs (Table 1A). The results of these studies were encouraging, though not entirely consistent. The original trial by Levitt and colleagues [24] used a within-subjects design to test the use of 5000–10,000 morning/afternoon lux-hours of "bright fluorescent light", continuing ADMs as per previous care. In this pilot test, seven of the 10 enrolled patients had an improvement of mood following BLT [24]. Following this initial proof of concept, eight between-subjects studies of the treatment were completed, of which seven indicated effectiveness. First, Schuchardt et al. [25], compared bright light (5000 lux-hours, daytime, wavelength not described) to dim light in 40 patients receiving fluoxetine, and saw a larger antidepressant response following bright light. Similarly, a second study of 29 patients found that three weeks of bright light (10,000 morning lux-hours, "cool white fluorescent") led to equivalent depressive symptomology decrease as imipramine treatment (by 9.1 and 6 HAM-D points, respectively), and that more patients in the BLT group responded (50% decrease in HAM-D score to a score <8) to treatment (66.7%) than did patients in either the imipramine group (33.3%) or the combination bright light and imipramine group (36.4%) [26]. Sertraline was also found to be effective in combination with BLT, with a significantly larger treatment response (50% decrease in HAM-D score to score <8) found in patients receiving bright light (10,000 morning lux-hours, "bright white fluorescent") than of those receiving dim light, over the course of bright light treatment [27,28]. Similarly, venlafaxine hydrochloride combined with BLT (7000 morning lux-hours, wavelength not provided) led to improved depressive symptoms over the drug alone [29]. A small trial of 15 patients found that there was no additional treatment benefit with the addition of fluoxetine to bright light (5000 morning lux-hours, "white fluorescent light") [30]. Finally, in the largest RCT to date, of 122 patients, both bright light alone (5000 morning lux-hours, "white fluorescent light" at 4000 K with power peaks at approximately 440, 490, 560, 590, 615, 630, and 715 nm) and bright light in combination with fluoxetine were shown to have a significantly larger effect than placebo treatments, while fluoxetine alone was not shown to be significantly different than placebo. Additionally, both response and remission rates were highest in the combination group [15].

In contrast, some studies have not supported the efficacy of adding bright light as an adjuvant to ADMs. First, as noted above, Prasko and colleagues found that bright light alone produced a greater benefit than bright light combined with imipramine [26]. Similarly, Muller et al. [31], found no group differences between trimipramine monotherapy, and trimipramine plus bright light (10,000 evening lux-hours). However, this is one of the few studies which used evening bright light, and thus may not be comparable to morning light.

Overall, the evidence suggests that morning BLT may be an effective adjunct treatment to ADMs. Typical lux-hours range from 5000 to 10,000, with therapy commenced not long after typical wake time. BLT was shown to be effective in as little as one week, though three to five weeks was more typical, and the longest range in a single trial was eight weeks. Further research investigating ideal treatment protocol (length, timing, duration) should be conducted in order to make clear clinical recommendations.

3.2. Bright light therapy as a stand-alone treatment option

Nine studies, spanning 1985–2013, investigated the use of BLT as a stand-alone treatment for depression (Table 1B). Additionally, three of the studies discussed previously investigated at least one stand-alone BLT group; one [15] which found the treatment to be beneficial, though not as beneficial as a combination of bright light and fluoxetine, another [30] which found no additional benefit of an ADM in addition to BLT, and the third [26] which found that stand-alone bright light was actually more effective than a combination of bright light and ADM (imipramine).

The literature regarding the use of BLT as a stand-alone treatment for depression is mixed. Two studies have shown that bright light treatment is more effective than a dim red light control. The first (1500–5000 morning/evening lux-hours, "cool white or Vitalight fluorescent") was a preliminary within-subjects study, which demonstrated significant improvement following bright but not dim light after five days [32]. The second, by Putilov and colleagues, was also within-subjects, and showed a significant improvement in depression scores after treatment with bright light (5000 afternoon lux-hours, "cool white incandescent light") after seven days [33]. Additionally, a third within-subjects study comparing pre- and post-treatment results on a self-report questionnaire also suggested that BLT (2500–5000 morning lux-hours, wavelength not described) was effective in ameliorating depressive symptoms [34]. Finally, another study demonstrated that bright light (10,000 morning lux hours, 3000 K fluorescent) was more effective than a low-density ion generator control after five weeks [35]. However, this study also showed that bright light was as

Table 1A
Characteristics of studies investigating the use of bright light therapy as an adjunct treatment to antidepressant medication. Effect sizes included where possible. *Structured Interview Guide for the Hamilton Depression Rating Scale − Seasonal Affective Disorders.

First author, year	*n*	Diagnosis	Medications	Lux	Treatment duration (wks:duration (h):start time)	Lux-hours	Control condition(s)	Primary depression outcome	Outcomes	Effect size
Levitt et al., 1991 [24]	10	Treatment resistant major depression (RDC)	Antidepressants as per treatment as usual	5000	2:1:06:00 to 07:00 if no response, additional 1 h in afternoon	5000−10,000	Within subjects	Hamilton Depression Rating Scale	7/10 improved following treatment	
Schuchardt et al., 1993 [25]	40	Treatment resistant major depression (DSM-III-R)	Fluoxetine (20 mg); other antidepressants for some patients	2500	4:2:08:00 to 20:00	5000	300 lux dim light	Unknown	Larger antidepressant response with bright light	
Muller et al., 1997 [31]	28	Major depressive disorder (DSM-III-R)	Trimipramine (200 mg) from day 3	5000	4:2:17:30 to 19:30	10,000	Five weeks of trimipramine vs. 5 weeks trimipramine + bright light for weeks 2−5	Hamilton Depression Rating Scale	No difference between groups in depression at week 2 Trimipramine monotherapy significantly more effective at week 5 ($p < 0.05$)	
Prasko et al., 2002 [26]	29	Recurrent major depressive disorder (DSM-III-R)	Imipramine (150 mg)	5000	3:2:06:00 to 08:00	10,000	Bright light + imipramine (A); bright light + placebo drug (B); dim red light (500 lux) + imipramine (C)	Hamilton Depression Rating Scale, Beck Depression Inventory (BDI), Montgomery Asberg Depression Rating Scale	Greater improvement after B than after A ($p < 0.05$ −0.01) Only the BDI showed a significant benefit of B over C ($p < 0.05$) Response rate after B 66.7%, C 33.3%, A 36.4%.	
Martiny, 2004 [27]	102	Major depressive disorder (DSM-IV)	Sertraline (50 mg), increments/reductions allowed, mianserin and oxazepam for some patients	10,000	5:1:before 10:00	10,000	Dim red light (50 lux), 30 min in morning	Hamilton Depression Rating Scale (SIGH-SAD*)	Bright light more effective from week 1 ($p < 0.05$) Bright light superiority maintained until week 5 ($p < 0.01$) Response in 40.7% of dim light patients and 66.7% of bright light patients by week 5 Remission in 14.8% of patients in dim light and 41.7% in bright light by week 5	
Martiny et al., 2006 [28] Follow-up from [27]	102	Major depressive disorder (DSM-IV)	Sertraline (50 mg), increments/reductions allowed, mianserin and oxazepam for some patients	10,000	5:1:before 10:00 Medication continued after wk 5 for 4 wks	10,000	Dim red light (100 lux), 30 min in morning	Hamilton Depression Rating Scale (SIGH-SAD*)	No significant difference between groups on response or remission at weeks 6 and 9	
Agargun et al., 2013 [30]	15	Major depressive episodes (DSM-IV)	Fluoxetine (20 mg)	10,000	1:0.5:07:00 to 08:00	5000	Bright light or bright light + Fluoxetine	Hamilton Depression Rating Scale, Beck Depression Inventory	No significant difference between groups after treatment	
Guzel Ozdemir et al., 2015 [29]	50	Major depressive disorder (DSM-IV-TR)	75−150 mg venlafaxine hydrochloride	7000	1:1:07:00	7000	Bright light + antidepressant vs. antidepressant	Hamilton Depression Rating Scale	Depression was lower in the combination group after 2−4 wks ($p < 0.05$) 76% combination vs. 44% drug group had “mild” depression after 4 wks ($p < 0.05$)	

(*continued on next page*)

Table 1A (*continued*)

First author, year	*n*	Diagnosis	Medications	Lux	Treatment duration (wks:duration (h):start time)	Lux-hours	Control condition(s)	Primary depression outcome	Outcomes	Effect size
Lam et al., 2016 [15]	122	Major depressive disorder (DSM-IV-TR)	Fluoxetine hydrochloride (20 mg/day) or placebo	10,000	8:0.5:07:00 to 08:00	5000	Bright light + placebo drug (A); fluoxetine + inactivated ion generator (B); bright light + fluoxetine (C); inactive ion generator + placebo (D)	Montgomery Asberg Depression Rating Scale	A and C more effective than D ($p = 0.006$; $p < 0.001$) No significant difference between B and D C more effective than B ($p = 0.02$) Response at wk 8: 75.9% of C, 50.0% of A, 29% of B and 33.3% of D Remission at wk 8: 58.6% of C, 43.8% of A, 19.4% of B and 30.0% of D	B vs. D: $d = 0.24$ A vs. D: $d = 0.80$ C vs. D: $d = 1.11$

effective as a high-density ion generator, and the previous study by Putilov et al., demonstrated that an active exercise control was more effective at reducing symptoms of depression than the bright light treatment [33].

Three studies investigating bright light, however, demonstrated it to be no more effective than dim light in reducing symptoms of depression. First, Deltito and colleagues used 5000 morning lux-hours (wavelength not described) for seven consecutive days and found no difference between groups [23]. Volz et al., also used 5000 morning lux-hours for seven consecutive days ("bright white light") and found no main effect of light group [36]. Finally, Lande et al., used 15,000 lux-hours for five consecutive days (wavelength not described), and found what they reported as a trend ($p < 0.05$) for bright light scores (but not dim light) to be reduced half-way through the treatment protocol [37].

It is worth noting that almost all of these studies of bright light as a stand-alone treatment used a much shorter treatment duration than those of studies measuring bright light as an adjunct treatment to ADMs (Table 1). Additionally, the treatment and study protocols vary, as do the comparison conditions (exercise, negative ions, dim light, within-subjects, etc.). Thus, before reaching conclusions regarding the efficacy of bright light alone as a treatment for depression, it is recommended that further research be conducted using a standard methodology and treatment protocol (eg, 10,000 lux for 30–60 min within 15 min of wake), and further that the treatment protocol be lengthened to several weeks to resemble those trials using BLT as an adjunct.

Finally, the remaining two studies of bright light as a stand-alone treatment option investigated the timing of the treatment itself as the question of interest. Here, too, results were inconclusive. The first study found a numerically larger reduction in symptoms of depression after seven days of morning light than evening light (5000 lux-hours, "cool-white" full-spectrum fluorescent light) [38], whereas the second found no difference in treatment outcomes after administering three days of morning bright light, evening bright light (both at 15,000 lux-hours, full-spectrum fluorescent light), or only dim light [39]. However, it is possible that the number of consecutive days was too short to definitively determine treatment effects. This, too, should be investigated further.

3.3. Bright light therapy in geriatric patients

Depression in geriatric patients is unfortunately common, with an estimated prevalence of 11.19% [40], contributing to negative health outcomes and premature death [41]. ADMs may be effective, however given the number of other medications that many geriatric patients are prescribed, as well as potential changes in pharmacokinetics over the life span, in many cases the prescription of ADMs is not ideal [41,42]. Thus, the use of bright light to treat depressive symptoms may be especially appealing in this population.

Three studies have investigated the use of BLT in geriatric patients (Table 2), two (comprising 10 and 89 patients respectively) comparing bright and dim light [41,43], and one ($n = 60$ patients) comparing bright light to a no treatment control [44]. The first used 5000 morning lux-hours (irregular full visual spectrum output) [41], the second 7500 of early morning lux-hours (blue-mist filter on fluorescent tubes) [43], and the third 4167 lux-hours in the morning (wavelength not described). The results of all three studies were consistent, with BLT lowering depression scores significantly more than the control condition after at least five days of treatment. Additionally, significantly more patients were treatment responders or went into remission following BLT in two of the three studies [41,43]. Overall, although BLT appears to be a potentially effective treatment in this population, due to the limited number of studies,

Table 1B
Characteristics of studies investigating the use of bright light therapy as a stand-alone treatment for depression. *Structured Interview Guide for the Hamilton Depression Rating Scale − Seasonal Affective Disorders.

First author, year	*n*	Diagnosis	Medications	Lux	Treatment duration (wks:duration (h):start time)	Lux-hours	Control condition(s)	Primary depression outcome	Outcomes	Effect size
Kripke et al., 1985 [32]	8	Major depressive disorders	Unknown	1500−2500	Five days:1 −2:05:00 to 06:00 and 21:00 to 22:00 for some	1500−5000	Dim red light, <50 lux (counterbalanced, within subjects)	Hamilton Depression Ratings, Beck Depression Inventory (modified − no sleep items)	Significant improvement on Day 5 after bright light ($p = 0.05$, 0.02) but not red light; direct comparison between groups not significant	
Deltito et al., 1991 [23]	11/17	Major depressive disorder or disorders not otherwise specified; dysthymia (DSM-III-R)	Psychotropic and hypnotic medication free	2500	1:2:within 1 h of wake	5000	400 lux dim light	Hamilton Depression Rating Scale (SIGH-SAD*)	No effect of light intensity on depressive outcome	
Volz et al., 1991 [36]	42	Major depressive disorder (RDC, ICD-9)	Psychotropic free, except 1000 mg chloralhydrate (max) for some patients	2500	1:2:07:00 to 09:00	5000	Dim red light (50 lux)	Hamilton Depression Rating Scale	No difference in depression improvement between groups	
Yamada et al., 1995 [38]	17/27	Major depressive disorder (DSM-III-R)	Psychotropic free	2500	1:2:06:00 to 08:00	5000	Morning or evening (18:00 to 20:00 h), bright or dim (500 lux, yellow) light	Hamilton Depression Rating Scale	Bright light led to greater improvement than dim light Numerically larger reduction after morning than evening light	
Gordijn et al., 1998 [39]	8	Major depressive disorder and dysthymia (DSM-III-R)	Psychotropic free	2500	Three days per condition:6:3 h in morning and 3 h in evening	15,000	Dim light (<10 lux); bright (morning) then dim (evening) light; dim (morning) then bright (evening) light (randomized crossover for latter two conditions)	Hamilton Depression Rating Scale, Beck Depression Inventory	No difference in depression reduction between the three groups	
Goel et al., 2005 [35]	32	Single episode major depressive disorder (DSM-IV)	Two patients on antidepressants, otherwise psychotropic, recreational drug and alcohol free	10,000	5:1:wake	10,000	High-density (A) or low-density (B) negative air ions	Hamilton Depression Rating Scale (SIGH-SAD*)	Largest change after bright light (53.7%) and A (51.1%) vs. B (16.4%); $p < 0.05$ Remission: 50% (bright light), 50% (A), 0% (B)	$h = 1.58$
Putilov et al., 2005 [33]	18/138	Major or minor depressive disorder or dysthymia (DSM-IV)	Psychotropic free	2500	1:2:14:00	5000	1 h physical exercise	Hamilton Depression Rating Scale	Exercise was more effective than bright light ($p < 0.001$) Bright light significantly improved depression ($p < 0.001$) Recovery: 0% after bright light, 33.3% after exercise	
Lande et al., 2011 [37]	20	Mild−severe depression (score ≥50) on Zung self-rating depression scale	Treatment as usual (individual and group therapy, leisure skills, medication management)	10,000	Five days:1.5:unknown	15,000	50 lux dim light	Zung Self-Rating Depression Scale	Scores reduced halfway through bright light treatment ($p < 0.05$) Depression was reduced for both groups over time ($p < 0.02$)	

(*continued on next page*)

Table 1B (*continued*)

First author, year	*n*	Diagnosis	Medications	Lux	Treatment duration (wks:duration (h):start time)	Lux-hours	Control condition(s)	Primary depression outcome	Outcomes	Effect size
Naus et al., 2013 [34]	48	Major depressive disorder (DSM-IV-TR)	No medications (bright light treatment before care as usual)	5000–10,000	Up to 3:0.5:08:00 to 10:00	2500–5000	Within subjects, within subgroups (melancholic vs. atypical)	Quick Inventory of Depressive Symptoms – Self Report 16	Bright light significantly improved depression at the end of treatment ($p < 0.05$) and 4 week follow-up ($p < 0.001$) Depression subtype didn't predict symptom improvement	$d = -0.53, -0.73$

more information is needed before making recommendations for use.

3.4. Bright light therapy in perinatal women

Perinatal depression (onset during pregnancy or first 12 months postpartum) has an estimated prevalence of 10–20% in pregnant and postpartum women. For many perinatal women, the treatment of depression with ADMs is not desirable due to potential side effects and the possibility of impacting the child through pregnancy and breastfeeding [45]. Thus, treatment with BLT may present an appealing treatment option for these women. However, to date, little research has been done in this population. Four studies were found studying the use of BLT in women in the perinatal period; one investigating postpartum and three investigating antepartum depression (Table 3). For women with postpartum depression, BLT (5000 lux-hours, wavelength not described) was not shown to be more effective than dim red light [46]. However, as only one study, with 15 patients, has investigated the use of BLT in postpartum depression, further research is required before making clinical recommendations.

Of the three studies investigating the use of bright light in antepartum depression, one [46] was within subjects, and two [48,49] compared the use of bright and dim light. While the within-subjects study showed a clinical benefit within three weeks following the use of diffuse white fluorescent bright light [47], the other two reports (using either diffuse broad-band fluorescent or fluorescent bright white light) [48,49] were somewhat conflicting regarding required treatment duration (5 vs. 10 weeks to see treatment benefits). In all three of these studies, treatment timing was 7000–10,000 lux-hours timed within 10 min of wake time. BLT in antepartum depression requires further research and validation as to ideal treatment length.

4. Sleep deprivation therapy

Sleep deprivation therapy (SDT) for unipolar depression entails depriving a depressed individual of some or all of their normal night's sleep for a specified number of nights. The amount and type of sleep that is restricted depends on the type of SDT that the patient is undergoing. It has been well-established that roughly 50% of depressed individuals who undergo total SDT (missing a full night's sleep for at least one night) respond with positive mood improvements the following day [50]. In a foundational 1990 review, Wu and Bunney [50] reviewed 61 studies of SDT involving over 1700 participants, and found that 59% of depressed individuals experienced profound decreases in depressive symptoms the day following SDT. SDT has also been shown to be effective for patients of varying depressive severity [51], and predictors of positive response to SDT are similar to those that predict response to ADMs [51,14]. Studies have also shown efficacy when partially sleep restricting patients, but the evidence for how much or at what time a patient should sleep is inconclusive for both total and partial sleep restriction [52].

One limitation of SDT alone is the high rate of relapse following recovery sleep (the first night's sleep, or nap, following the SDT). Following recovery sleep, only 5–12% of patients show a sustained positive mood response [50,14], though this can be improved by co-administration of ADMs [14], and may be dependent on nap timing [53]. Some patients have also been shown to develop tolerance to treatment effects after multiple days of sleep restriction [14]. Of patients who do not develop tolerance, many may be unwilling to continue the protocol repeatedly due to resulting increased fatigue and sleepiness the next day. Given that no single sleep deprivation treatment has shown sustainability as a stand-alone treatment

Table 2
Characteristics of studies investigating the use of bright light therapy as a treatment for depression in geriatric adults. *Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorders, ΔNumber needed to treat.

First author, year	*n*	Diagnosis	Medications	Lux	Treatment duration (wks:duration (h):start time)	Lux-hours	Control condition(s)	Primary depression outcome	Outcomes	Effect size
Sumaya et al., 2001 [41]	10	Moderate to severe depression (Geriatric Depression Scale)	Antidepressant free	10,000	Five days:0.5:09:30 to 12:00	5000	300 lux placebo and no treatment controls [within subjects, randomized, crossover]	Geriatric Depression Scale	Depression score significantly lower after bright light ($p < 0.01$), but not the other conditions 50% of patients were no longer in the depressed range of scores after bright light	
Lieverse et al., 2004 [43]	89	Major depressive disorder (DSM-IV)	33–38% used antidepressants	7500	3:1:early morning	7500	Dim red light, approximately 50 lux	Hamilton Depression Rating Scale (SIGH-SAD*)	Bright light led to more improvement in depression than control after 3 weeks (43% vs. 36%, $p = 0.03$) Bright light led to more improvement in depression than control at 3-week post treatment follow-up (54% vs. 33%, $p = 0.001$) 58% of bright light group responded at follow-up, vs. 34% of placebo ($p = 0.05$)	$d = 0.5$ $d = 0.93$ $NNT^{\Delta} = 5$
Tsai et al., 2004 [44]	60	Major depressive disorder or disorders (DSM-IV)	Psychotropic free	5000	Five days:0.83:09:00 to 12:00	4167	No treatment	Geriatric Depression Scale	Significantly lower depression after bright light but not control ($p = 0.000$)	

Table 3
Characteristics of studies investigating the use of bright light therapy as a treatment for depression in pregnant and post-partum women. *Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorders or #Atypical Depression Supplement.

First author, year	*n*	Diagnosis/state	Medications	Lux	Treatment duration (wks:duration (h):start time)	Lux-hours	Control condition (s)	Primary depression outcome	Outcomes	Effect size
Oren et al., 2002 [47]	16	Major depressive disorder (DSM-IV); pregnant women	Psychotropic free	10,000	3:1:within 10 min of wake	10,000	Within subjects (Control–TX –Control)	Hamilton Depression Rating Scale (SIGH-SAD*)	Patients improved by 49% after 3 weeks ($p < 0.001$); 8 of 16 improved by >50% Patients who completed 5 weeks of treatment improved by 59% ($p < 0.05$); 4 of 7 participants increased by >50% and achieved complete remission	
Epperson et al., 2004 [48]	10	Major depressive disorder (DSM-IV); pregnant women	Psychotropic free	7000	5:1:within 10 min of wake; option of extending to 10: 1.25	7000–8750	500 lux light box	Hamilton Depression Rating Scale (SIGH-SAD*)	No significant difference between groups at 5 weeks Over 10 weeks of individual dosing ($n = 3$), significant effect of bright light ($p = 0.001$)	0.43
Corral et al., 2007 [46]	15	Major depressive disorder, post-partum onset; post-partum women	Antidepressant free	10,000	6:0.5:07:00 to 09:00	5000	600 lux red light	Hamilton Depression Rating Scale (SIGH-SAD*)	No significant difference between groups in improvement	
Wirz-Justice et al., 2011 [49]	27	Major depressive disorder (DSM-IV); pregnant women	Stable, previous antidepressant use allowed	7000	5:1:within 10 min of wake	7000	70 lux dim red light	Hamilton Depression Rating Scale (SIGH-ADS#)	Significant effect of all factors on improvement in depression ($p < 0.05$) Significantly greater treatment effect and % improvement in bright light group ($p < 0.05$)	Pillai $V = 0.403$

Table 4
Characteristics of studies investigating the use of combined chronotherapies to treat depression in the general population. *Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorders – Self Report; #total sleep deprivation; ΔHamilton Depression Rating Scale, ◊Montgomery Asberg Depression Rating Scale.

First author, year	*n*	Diagnosis	Medications	BL treatment duration	Lux-hours	Other therapy 1	Other therapy 2	Other therapy 3	Control condition(s)	Primary depression outcomes	Study outcomes
Kripke et al., 1983 [57]	12	"Depressed"	Most were "drug free"	1 h per night	1000–2000	Three consecutive nights: Night 1: woke 1 –2 h before normal wake, with BLT	Night 2: woke 1 –2 h before normal wake with dim red light	Night 3: woke 2 –3 h after bedtime with dim red light	Counterbalanced, within subjects	ΔHamilton Depression Rating Scale (HAM-D), Beck Depression Inventory	HAM-D significantly lower after bright than dim light ($p < 0.05$) Significantly lower Hamilton ratings at 1-week follow-up compared to baseline
Vollmann & Berger, 1993 [58]	17	Major depressive disorder melancholia subtype (DSM-III-R)	Most on antidepressants for >1 month and treatment resistant	n/a	n/a	One night total sleep deprivation (TSD#)	Phase advance following TSD, starting at 5 pm and shifting toward midnight by 1 h each day, for 7 days	n/a	Within subjects	HAM-D	Nine patients were responders to TSD: none relapsed during phase advance Non-responders to TSD did respond to phase advance
Loving et al., 2002 [59]	13	Major depressive disorder (DSM-IV), resistant to treatment	Antidepressants	One week, 0.5 h, 06:00 to 09:00 start	5000	Late partial wake therapy, woken at 3:00 am, at home; first day of bright light started immediately	n/a	n/a	Dim red light (100 lux)	Hamilton Depression Rating Scale (SIGH-SAD-SR*)	Significant difference between groups (outlier patient who improved following dim red light was removed); $p < 0.025$
Putilov et al., 2005 [33]	35/138	Major or minor depressive disorder or dysthymia (DSM-IV)	Psychotropic free	1:2:14:00	5000	One night total sleep deprivation (TSD)	n/a	n/a	TSD + 1 h physical exercise or (A) 1 h physical exercise under bright light (B) or 1 h physical exercise (C)	HAM-D	TSD + bright light less effective than A ($p = 0.013$) and B (trend; $p = 0.077$) TSD + bright light equally effective as C
Moscovici & Kotler, 2009 [60]	12	At least 4 main criteria symptoms of major depressive episode (ICD-10)	Antidepressant free for 5 wks	Four days, 1 h per day upon wake	7500	Partial sleep deprivation, woke at 2:30 am day 1, 3:00 am days 2–4	Each day: dawn simulation to wake; green light (525 nm) immediately following	Sleep phase advance (7:00 pm bedtime), days 2–4	Bright light significantly improved depression ($p < 0.001$) Recovery: 0% after bright light, 33.3% after exercise	HAM-D, ◊Montgomery Asberg Depression Rating Scale (MADRS), Zung Self-Rating Depression Scale	All patients improved: HAM-D ($p < 0.001$), MADRS ($p < 0.001$), Zung ($p < 0.001$) Improvement was not lost at follow-up
Sahlem et al., 2014 [61]	10	Unipolar depression; suicidal ideation	Antidepressants	Four days, 0.5 h, 06:00 to 08:00 start	5000	One night total sleep deprivation (TSD)	Three days of sleep phase advance following TSD (sleep window 6pm –1am; 8pm–3am; 10pm–5am)	n/a	Within subjects	HAM-D	Significant decrease in HAM-D score from baseline 60% of patients met HAM-D remission criteria at the end of the study
Dallaspezia & Jaarsveld, 2016 [62]	27	Major depressive disorder (DSM-IV)	Antidepressant free	Five days after sleep deprivation: 0.5: morning (chronotype based)	5000	One night total sleep deprivation (TSD)	n/a	n/a	Within subjects	Beck Depression Inventory	Remission: 37% 1 week after treatment, 55% 3 months after treatment Depression scores decreased during treatment ($p < 0.00001$)

strategy, sleep deprivation is likely a more useful strategy when used in combination with other chronotherapeutics, as discussed in following sections.

5. Sleep phase advance

Sleep phase advance is a circadian treatment for depression. With this treatment the circadian rhythm is shifted, such that patients wake up and go to bed earlier in a 24-h period than they previously would. Advancing the sleep phase is often a by-product of BLT, but may be addressed in CBT-I, and has usually been used in combination with total SDT in order to prolong its antidepressant effects. Sleep phase advance as a stand-alone treatment has minimal evidence as to its efficacy for patients with unipolar depression. Most classic studies touting the treatment include at least some bipolar patients as study participants [54–56].

6. Combination treatments

6.1. Combination chronotherapeutic treatments in the general population

These chronotherapeutic treatments have also been used together in combination, and in combination with ADMs, in order to reduce treatment limitations and enhance therapeutic effects. Only a handful of studies on this topic has been completed, most within-subjects and with small sample sizes (the largest of which had 35 patients; Table 4).

The earliest of these studies, investigating 1-h night-time awakenings in bright (1000–2000 lux-hours, "warm white fluorescent") vs. dim red light, found mixed results. While depression scores were significantly lower after bright as compared to dim light, there were no significant changes from baseline measurements during the night time awakenings, though there was a significant improvement compared to baseline at one week follow-up on the Hamilton depression ratings (but not in Beck ratings) [57]. Another of the studies found mixed, but encouraging results; while total sleep deprivation and bright light (5000 lux-hours, "cool white incandescent") did lower depression ($p = 0.002$), and led to a 25% recovery rate, it did not lower depression as much as a combination of total sleep deprivation and exercise (75% recovery; $p < 0.05$) [33]. The other five studies on the topic found positive results. The first, by Vollmann and Berger [58], had a 53% response rate to total sleep deprivation, as measured in Hamilton Depression Rating Scale scores. None of these responders had a relapse in depressive symptoms following a week of subsequent sleep phase advance. Notably, the 47% of patients who did not respond to total sleep deprivation had improvement in their depressive symptoms following sleep phase advance therapy [58].

Loving et al. [59], tried a similar technique, using BLT following partial sleep deprivation. This study found that the group treated with bright white light (5000 lux-hours) improved significantly more than the group treated with dim red light, with the exception of one patient who responded to red light. All of these patients were treated with ADMs [59]. In a study of patients not taking ADMs, a combination of chronotherapeutics including partial sleep deprivation, dawn simulation and BLT (7500 lux-hours, increase of white light, followed by 525 nm green light, followed by broad spectrum light) were found to improve symptoms of depression and maintain these improvements at four-week follow-up [60]. Finally, sleep phase advance and BLT (5000 lux-hours, wavelength not described) following total sleep deprivation were shown to significantly decrease depressive scores and result in a high rate of remission in patients currently

Table 5
Characteristics of studies investigating the use of combined chronotherapies to treat depression in geriatric patients (59–80 yrs old). *Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorders – Self Report.

First author, year	*n*	Medications	Brightness (lux)	BLT duration (wks:duration (h):start time)	Lux-hours	Color/ temperature	Other therapy	Control condition (s)	Primary depression outcome measure	Outcomes
Loving et al., 2005 [42]	81	Treatment as usual (37% took antidepressants)	8500	4:1:morning or mid-day or evening (chronotype based)	8500	Bright white	Wake therapy (late partial, 4 h sleep duration) prior to light therapy	Dim red light (<10 lux) + wake therapy	Hamilton Depression Rating Scale (SIGH-SAD-SR*), Geriatric Depression Scale	No significant differences between groups following treatment Few participants were able to complete wake therapy as directed
Loving et al., 2005 [63]	33	Treatment as usual (39% took antidepressants)	1200	4:1:1 h of wake	1200	Bright green	Wake therapy (late partial, 4 h sleep duration) prior to light therapy	10 lux dim red light + wake therapy	Hamilton Depression Rating Scale (SIGH-SAD-SR*), Geriatric Depression Scale	No significant difference between groups No significant improvement following wake therapy

medicated following their treatment-as-usual. In addition, these patients endorsed suicidal ideation at the beginning of the trial protocol, and there was a significant decrease in this suicidal ideation by the end of the treatment period [61]. Total sleep deprivation followed by BLT (5000 lux-hours, wavelength not described) was also shown to reduce symptoms of depression in un-medicated patients, leading to a 55% rate of remission three months after the end of the treatment [62].

These results indicate that combining these chronotherapies may result in a more efficacious and prolonged antidepressant effect than using any one of these treatments uniquely. However, until randomized controlled research is conducted comparing the efficacy of these combined treatments to current standard-of-care treatments, the true benefit of these combined treatments is unclear.

6.2. Combination chronotherapeutic treatments in geriatric patients

Only two studies, by the same researchers, investigated the use of combined chronotherapeutic treatments in geriatric patients (Table 5). Neither provided support for the use of these treatments in this population. Both used late partial wake therapy followed by bright light (8500 lux-hours, 400–625 nm (approx.) white [42] or 1200 lux-hours 500 nm (approx.) green [63] or a dim red light control. In both cases, there was no significant difference in depression scores following treatment, and there was no immediate improvement in depressive symptomology immediately following wake therapy [42,63]. When compared to results of BLT as a stand-alone treatment in this population, these results would seem to imply that BLT alone is more effective than BLT in combination with other chronotherapeutics. However, given that these two studies compared wake therapy and BLT to wake therapy and dim red light, the unique effects of the chronotherapeutics compared to a non-chronotherapeutic control cannot be determined. The only conclusion that can be drawn is that BLT as an adjunct to wake therapy does not lead to significantly better therapeutic outcomes than wake therapy and a control light condition. Until more research is conducted, recommendations regarding combined chronotherapies in this population cannot be made at this time.

7. Conclusions

Given the downsides of ADMs such as the long time to response [3–5] and concerns in some populations regarding ADM use, alternative treatments for depression must be sought. Chronotherapies have several advantages that target these areas, often including a large and rapid response and fewer side effects.

However, chronotherapies also have limitations which should be considered. Sleep deprivation, either on its own or as a part of other therapies (eg, CBT-I, combination therapies) should be undertaken with caution, as it can induce daytime sleepiness and attentional impairment. Additionally, sleep deprivation and sleep phase advance are of limited use as stand-alone chronotherapies given the high rates of rapid relapse following recovery sleep, and the difficulty in maintaining the treatment regimen. BLT can have side effects, though these are usually transient and mild, and usually thought to be less severe than many ADMs. They may include headaches, eyestrain, sedation, restlessness, changes in appetite or nausea, or vertigo [31,8]. Finally, it is important to consider whether a given chronotherapy or combination thereof is appropriate for a patient and their ability to carry out the therapy at home, given the time- and effort-consuming nature of many of the treatments discussed.

This paper has extensively reviewed BLT and combination chronotherapies, which show varying degrees of promise in treating unipolar depression. BLT is a promising adjunct treatment to ADMs, and may also be effective as a stand-alone treatment. However, further research is required, for example regarding effects of cumulative light exposure, or of the timing, duration, and length of treatment. Of note, few of the reviewed studies considered patient chronotype when scheduling treatment timing. Future studies should investigate whether administering light at an optimal time for each patient's chronotype could lead to improved treatment outcomes. Combination chronotherapies also show promise, but a clearer notion of which combination and dosage is ideal for which patient is needed, and further research with standardized methodology is required. Additionally, further research elucidating the role of ADMs in addition to these combined chronotherapies is recommended. Further research (notably RCTs) on optimal combination treatment protocols is severely needed, especially before the suggestion of any clinical standard of care.

Practice points

- Bright light therapy shows promise as an effective adjunct to treatment with antidepressant medications. Based on the limited data available, bright light exposure for 5000–10,000 lux-hours soon after waking for several weeks would most likely improve symptoms, although more research is required in order to make specific recommendations.
- Sleep deprivation therapy should be undertaken with caution in individuals who will be performing tasks such as driving, operating heavy machinery, etc. on the day following treatment. It is possible that during this period, patients will have difficulty concentrating, and may experience sleepiness and decreased productivity, though improved mood may counter these effects.
- Combined chronotherapies may be more efficacious than the separate treatment components individually, especially in the case of sleep phase advance and wake therapy (which often leads to depressive relapse immediately following recovery sleep). However, further research is required before making recommendations.

Research agenda

- It is recommended that further research be conducted using a standard methodology and treatment protocol for bright light as a treatment for depression, likely using a treatment protocol spanning several weeks.
- Research is required regarding the use of bright light therapy and combined chronotherapies in postpartum and anti-partum depression, as well as in geriatric patients.
- Sleep phase advance has shown some benefit in bipolar patients; research using sleep phase advance to improve depression in unipolar patients is recommended.
- Until randomized controlled research is conducted comparing the efficacy of combined treatments to stand-alone chronotherapies, and to current standard-of-care treatments, the true benefit of these combined treatments is unclear. Such research is recommended, as these areas show promise in the rapid and sustained treatment of depression.

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Conflicts of interest

None.

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References

[1] Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). J Am Med Assoc 2003;289(23):3095–105.
[2] Khan A, Brown WA. Antidepressants versus placebo in major depression: an overview. World Psychiatr 2015;14(3):294–300.
[3] Quitkin FM, Rabkin JG, Ross DC, et al. Duration of antidepressant drug treatment: what is an adequate trial? Arch Gen Psychiatry 1984;41(3):238–45.
[4] Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. J Clin Psychiatry 2005;66:148–58.
[5] Quitkin FM, McGrath PJ, Stewart JW, et al. Accurate meta-analytical assessment of "true antidepressant effects" needed. J Clin Psychiatry 2005;66(09):1192–3.
[6] Tsuno N, Besset A, Ritchie K. Sleep and depression. J Clin Psychiatry 2005;66(10):1254–69.
[7] Franzen PL, Buysse DJ. Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. Dialogues Clin Neurosci 2008;10(4):473–81.
[8] Germain A, Kupfer DJ. Circadian rhythm disturbances in depression. Hum Psychopharmacol 2008;23(7):571–85.
[9] Antypa N, Vogelzangs N, Meesters Y, et al. Chronotype associations with depression and anxiety disorders in a large cohort study. Depress Anxiety 2016;33(1):75–83.
[10] Swanson LM, Burgess HJ, Huntley ED, et al. Relationships between circadian measures, depression, and response to antidepressant treatment: a preliminary investigation. Psychiatry Res 2017;252:262–9.
[11] Haynes PL, Ancoli-Israel S, McQuaid J. Illuminating the impact of habitual behaviors in depression. Chronobiol Int 2005;22(2):279–97.
[12] aan het Rot M, Moskowitz DS, Young SN. Exposure to bright light is associated with positive social interaction and good mood over short time periods: a naturalistic study in mildly seasonal people. J Psychiatr Res 2008;42(4):311–9.
[13] Rosenthal NE, Sack DA, Gillin JC. Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry 1984;41(1):72–80.
[14] Benedetti F, Barbini B, Colombo C, et al. Chronotherapeutics in a psychiatric ward. Sleep Med Rev 2007;11(6):509–22.
[15] Lam RW, Levitt AJ, Levitan RD, et al. Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder: a randomized clinical trial. JAMA Psychiatry 2016;73(1):56–63.
[16] Westrin A, Lam RW. Seasonal affective disorder: a clinical update. Ann Clin Psychiatry 2007;19(4):239–46.
[17] Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. Cochrane Database Syst Rev 2004;2:CD004050.
[18] Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry 2005;162(4):656–62.
[19] Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. CNS Spectr 2005;10(8):647–63. quiz 672.
[20] Even C, Schroder CM, Friedman S, et al. Efficacy of light therapy in nonseasonal depression: a systematic review. J Affect Disord 2008;108(1–2):11–23.
[21] Martensson B, Pettersson A, Berglund L, et al. Bright white light therapy in depression: a critical review of the evidence. J Affect Disord 2015;182:1–7.
[22] Al-Karawi D, Jubair L. Bright light therapy for nonseasonal depression: meta-analysis of clinical trials. J Affect Disord 2016;198:64–71.
[23] Deltito JA, Moline M, Pollak C, et al. Effects of phototherapy on non-seasonal unipolar and bipolar depressive spectrum disorders. J Affect Disord 1991;23(4):231–7.
[24] Levitt AJ, Joffe RT, Kennedy SH. Bright light augmentation in antidepressant nonresponders. J Clin Psychiatry 1991;52(8):336–7.
[25] Schuchardt HM, Kasper S, Ruhrmann S. Is light therapy able to enhance the antidepressant effect of fluoxetine in patients with non-seasonal major depression? Pharmacopsychiatry 1993;26:201.
[26] Prasko J, Horacek J, Klaschka J, et al. Bright light therapy and/or imipramine for inpatients with recurrent non-seasonal depression. Neuroendocrinol Lett 2002;23(2):109–13.
[27] Martiny K. Adjunctive bright light in non-seasonal major depression. Acta Psychiatr Scand 2004;110(Suppl. 425):7–28.
[28] Martiny K, Lunde M, Unden M, et al. The lack of sustained effect of bright light, after discontinuation, in non-seasonal major depression. Psychol Med 2006;36(9):1247–52.
[29] Guzel Ozdemir P, Boysan M, Smolensky MH, et al. Comparison of venlafaxine alone versus venlafaxine plus bright light therapy combination for severe major depressive disorder. J Clin Psychiatry 2015;76(5):e645–54.
[30] Agargun MY, Sayar GH, Bulut H, et al. Comparison of effects of bright light therapy alone or combined with fluoxetine on severity of depression, circadian rhythms, mood disturbance, and sleep quality, in patients with non-seasonal depression. Chronophysiol Ther 2013;3:53–9.
[31] Muller MJ, Seifritz E, Hatzinger M, et al. Side effects of adjunct light therapy in patients with major depression. Eur Arch Psychiatry Clin Neurosci 1997;247:252–8.
[32] Kripke DF, Gillin JC, Mullaney DJ, et al. Five-day bright white light treatment of major depressive disorders. Sleep Res 1985;14:132.
[33] Putilov AA, Pinchasov BB, Poljakova EY. Antidepressant effects of mono- and combined non-drug treatments for seasonal and non-seasonal depression. Biol Rhythm Res 2005;36(5):405–21.
[34] Naus T, Burger A, Malkoc A, et al. Is there a difference in clinical efficacy of bright light therapy for different types of depression? A pilot study. J Affect Disord 2013;151(3):1135–7.
[35] Goel N, Terman M, Su Terman J, et al. Controlled trial of bright light and negative air ions for chronic depression. Psychol Med 2005;35(7):945–55.
[36] Volz HP, Mackert A, Stieglitz RD, et al. Diurnal variations of mood and sleep disturbances during phototherapy in major depressive disorder. Psychopathology 1991;24(4):238–46.
[37] Lande RG, Williams LB, Gragnani C, et al. Effectiveness of light therapy for depression among active duty service members: a nonrandomized controlled pilot trial. Complement Ther Med 2011;19(3):161–3.
[38] Yamada N, Martin-Iverson MT, Daimon K, et al. Clinical and chronobiological effects of light therapy on nonseasonal affective disorders. Biol Psychiatry 1995;37(12):866–73.
[39] Gordijn MC, Beersma DG, Korte HJ, et al. Testing the hypothesis of a circadian phase disturbance underlying depressive mood in nonseasonal depression. J Biol Rhythms 1998;13(2):132–47.
[40] Steffens DC, Fisher GG, Langa KM, et al. Prevalence of depression among older Americans: the aging, demographics and memory study. Int Psychogeriatr 2009;21(5):879–88.
[41] Sumaya IC, Rienzi BM, Deegan 2nd JF, et al. Bright light treatment decreases depression in institutionalized older adults: a placebo-controlled crossover study. J Gerontol A Biol Sci Med Sci 2001;56(6):M356–60.
[42] Loving RT, Kripke DF, Elliott JA, et al. Bright light treatment of depression for older adults [ISRCTN55452501]. BMC Psychiatry 2005;5:41.
[43] Lieverse R, Van Someren EJ, Nielen MM, et al. Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. Arch Gen Psychiatry 2011;68(1):61–70.
[44] Tsai YF, Wong TK, Juang YY, et al. The effects of light therapy on depressed elders. Int J Geriatr Psychiatry 2004;19(6):545–8.
[45] Crowley SK, Youngstedt SD. Efficacy of light therapy for perinatal depression: a review. J Physiol Anthropol 2012;31(15):15.
[46] Corral M, Wardrop AA, Zhang H, et al. Morning light therapy for postpartum depression. Arch Womens Ment Health 2007;10(5):221–4.
[47] Oren DA, Wisner KL, Spinelli M, et al. An open trial of morning light therapy for treatment of antepartum depression. Am J Psychiatry 2002;159(4):666–9.
[48] Epperson CN, Terman M, Terman JS, et al. Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J Clin Psychiatry 2004;65(3):421–5.
[49] Wirz-Justice A, Bader A, Frisch U, et al. A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. J Clin Psychiatry 2011;72(7):986–93.
[50] Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. Am J Psychiatry 1990;147(1):14–21.
[51] Voderholzer U. Sleep deprivation and antidepressant treatment. Dialogues Clin Neurosci 2003;5(4):366–9.
[52] Dallaspezia S, Suzuki M, Benedetti F. Chronobiological therapy for mood disorders. Curr Psychiatry Rep 2015;17(12):95.
[53] Wiegand M, Riemann D, Schreiber W, et al. Effect of morning and afternoon naps on mood after total sleep deprivation in patients with major depression. Biol Psychiatry 1993;33(6):467–76.
[54] Wehr TA, Wirz-Justice A, Goodwin FK, et al. Phase advance of the circadian sleep–wake cycle as an antidepressant. Science 1979;206(4419):710–3.
[55] Souetre E, Salvati E, Pringuey D, et al. Antidepressent effects of the sleep/wake cycle phase advance. J Affect Disord 1987;12:41–6.
[56] Riemann D, Konig A, Hohagen F, et al. How to preserve the antidepressive effect of sleep deprivation: a comparison of sleep phase advance and sleep phase delay. Eur Arch Psychiatry Clin Neurosci 1999;249:231–7.

[57] Kripke DF, Risch SC, Janowsky DJ. Lighting up depression. Psychopharmacol Bull 1983;19(3):526–30.
[58] Vollmann J, Berger M. Sleep deprivation with consecutive sleep-phase advance therapy in patients with major depression: a pilot study. Biol Psychiatry 1993;33(1):54–7.
[59] Loving RT, Kripke DF, Shuchter SR. Bright light augments antidepressant effects of medication and wake therapy. Depress Anxiety 2002;16(1):1–3.
[60] Moscovici L, Kotler M. A multistage chronobiologic intervention for the treatment of depression: a pilot study. J Affect Disord 2009;116(3):201–7.
[61] Sahlem GL, Kalivas B, Fox JB, et al. Adjunctive triple chronotherapy (combined total sleep deprivation, sleep phase advance, and bright light therapy) rapidly improves mood and suicidality in suicidal depressed inpatients: an open label pilot study. J Psychiatr Res 2014;59:101–7.
[62] Dallaspezia S, van Jaarsveld A. Antidepressant chronotherapeutics in a group of drug free outpatients. Psychiatry Res 2016;241:118–21.
[63] Loving RT, Kripke DF, Knickerbocker NC, et al. Bright green light treatment of depression for older adults [ISRCTN69400161]. BMC Psychiatry 2005;5:42.